PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3838PTWO/AG/la	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/051226	International filing date *(day/month/year)* 24.06.2004	Priority date *(day/month/year)* 26.06.2003
International Patent Classification (IPC) or national classification and IPC A61K9/22		
Applicant MEDIOLANUM PHARMACEUTICALS LTD.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.04.2005	22.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Muller, S Telephone No. +31 70 340-2080

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/051226

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-11 as originally filed

   Claims, Numbers

   1-17 received on 25.04.2005 with letter of 22.04.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

It appears that an obvious mistake has been made in claims 5-10 which refer to a "plasticized ethanol" instead of a "plasticized PLGA".
In order to accelerate the procedure, the present communication is based on claims 5-10 referring to a "plasticized PLGA".

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited Documents

The following documents are referred to in this communication:

D1: US-A-5 520 923 (NORTHEY RICHARD P ET AL) 28 May 1996 (1996-05-28)
D2: WO 03/041685 A (ALZA CORP) 22 May 2003 (2003-05-22)
D3: WO 00/33809 A (MARION PIERRE ;MAQUIN ALAIN (FR); MAURIAC PATRICE (FR); MEDIOLANUM) 15 June 2000 (2000-06-15)

2. Novelty

The present application appears to be new over the prior art, because no document of the prior art discloses the platicized PLGA of claim 1, which is prepared by extrusion and final grinding of the extruded mixture.

D1 discloses (see column 2, line 46 - column 3, line 13 and column 7, lines 50-57) the addition of ethanol to PLGA in the preparation of a sponge. The structure of such a sponge is different to that of the plasticized PLGA of claim 1, which is in powder form.

D2 discloses (see examples 1-4 on pages 25-29) implantable gels comprising PLGA and ethanol as thixotropic agent. This gel does not anticipate the present plasticized PLGA

which is in powder form.

D3 discloses (see examples 1 on pages 7-9) a process for preparing subcutaneous implants comprising: a) wet granulating a mixture comprising avoreline and PLGA with ethanol, b) drying the granules, c) extruding the dried granules having an ethanol content of 0,66% w/w. D3 does not anticipate the plasticized PLGA claimed in present claim 1, which is an intermediate product in a powder form and does not contain any active principle.

The subject-matter of claim 1 is therefore new (Article 33(2) PCT).

3. Inventive Step

D1 is considered as being the closest prior art. It discloses (see column 2, line 46 - column 3, line 13 and column 7, lines 50-57) the addition of a mixture of surfactant and ethanol to PLGA in the preparation of a sponge. The mixture of ethanol and surfactant is added to the PLGA particles to act as an external plasticizer and to lower the Tg of the PLGA (see column 10, lines 8-10).
The PLGA of the present application differs to that of D1 in that it is in form of a powder instead of a sponge.
Such a plasticized PLGA in powder form is to be used in a process for making subcutaneous implants comprising extrusion. The plasticized PLGA having a lower Tg permits the extrusion temperature to be reduced (see page 3, lines 4-15).
The objective problem of the present application may therefore be regarded as the provision of a PLGA polymer having a lower Tg which could be used in extrusion for making subcutaneous implants.
Neither D1 nor any document of the prior art suggests the use of ethanol for reducing the Tg of PLGA in a powder form.
Consequently, the subject-matter of claims 1-17 is inventive over the prior art (Article 33(3) PCT).

4. Industrial applicability

Claims 1-17 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.

NEW SET OF CLAIMS

1.PLGA plasticized with ethanol, obtained with a process comprising the following steps:

a) grinding PLGA to obtain a ground product in which the particles have dimensions less than 250 μm;

b) adding ethanol to the ground product obtained in the preceding stage in concentrations between 5 and 20 parts by weight/weight of PLGA and heating the mixture obtained to a temperature between 45 and 65°C, until a viscous and stable gel is obtained;

c) drying the product coming from step (b),

d) grinding the dried product obtained at a temperature ranging from –20 and +5°C;

e) optionally mixing the product originating from the preceding stage with PLGA as such which has been previously ground until a ground product of particle size less than 250 μm is obtained, in weight ratios between 10:90 and 99:1, at a temperature between –20 and +5°C,

f) extruding the aforesaid mixture at 75°C,

g) grinding the extruded product at a temperature between -20°C and +5°C.

2. Plasticized PLGA as claimed in claim 1 containing ethanol in concentrations between 2 and 15 % by weight on the weight of PLGA.

3. Plasticized PLGA as claimed in claim 2 wherein said ethanol concentrations are comprised between 3 and 10% by weight on the weight of PLGA.

4. Plasticized PLGA as claimed in claim 2 in which said concentrations are between 5 and 10% by weight on the weight of PLGA.

5.Plasticised ethanol according to anyone of claims 1-4, wherein in stage (b) the ethanol is added in a quantity of 10 parts by weight/weight of PLGA.

6.Plasticised ethanol according to anyone of claims 1-5, wherein in stage (d) the drying is conducted until obtaining an ethanol concentration in PLGA comprised between 10 and 30%/by weight/PLGA weight.

7. Plasticised ethanol according to claim 6 wherein said ethanol concentration is 20% by weight/PLGA weight.

8. Plasticised ethanol according to claim 6 or 7, wherein said drying is carried out

at a temperature comprised between 20 and 25°C under an air stream.

9. Plasticised ethanol as claimed in anyone of claims 1-8, wherein the grinding temperature in stage (d), (e) and (g) is -10°C.

10. Plasticised ethanol as claimed in anyone of claims 1-9 wherein in stage (e) the weight ratio of PLGA originating from stage (d)/PLGA as such is comprised between 16:84 and 40:60.

11. Subcutaneous implants obtained by extrusion, containing the active principle dispersed in PLGA plasticized with ethanol as claimed in any one of claims 1-10.

12. Subcutaneous implants as claimed in claim 11 containing thermolabile active principles.

13. Subcutaneous implants as claimed in claim 12, wherein said thermolabile active principles are chosen from the class consisting of: proteins, vaccines, antibodies and vectors for genic therapy.

14. A process for preparing the subcutaneous implants according to anyone of claims 11-13 comprising the following stages:

i)mixing the active principle with the plasticized PLGA as claimed in any one of claims 1-10, at a temperature between -20°C and +5°C,

ii)extruding the ground product originating from stage (i) at a temperature less than 70°C.

15. The process as claimed in claim 14, wherein the temperature of stage (i) is -10°C.

16. The process as claimed in anyone of claims 14 and 15 wherein the temperature of stage (ii) is less than 60°C when plasticized PLGA containing when plasticized PLGA containing ethanol at concentrations between 3 and 4% by weight on the weight of PLGA is used in stage (i).

17. The process as claimed in anyone of claims 15 and 16,wherein the temperature of stage (ii) is equal to 40°C, when plasticized PLGA containing ethanol at concentrations between 5 and 10% by weight/ weight of PLGA is used.